Topical oxygen treatment relieves pain from hard-to-heal leg ulcers and improves healing: a case series

Abstract: Managing painful hard-to-heal leg ulcers is challenging with current therapeutic options. Wounds are prone to being hypoxic, and the subsequent pain is often related to hypoxia. Hyperbaric oxygen therapy (HBOT) is used to treat hard-to-heal leg wounds by delivering 100% oxygen at a pressure 2–3 times higher than atmospheric pressure. Unfortunately, most patients cannot be offered HBOT because it is costly and needs to be applied at specialised centres. Therefore, topical continuous oxygen therapy (TCOT) is a novel alternative for continuous local oxygen delivery to wounds and is associated with improved wound healing; however, its effect on painful wounds is unknown. This retrospective study was conducted on 20 patients, of whom 17 had painful hard-to-heal leg ulcers. In 13 patients (76%) with painful ulcers, TCOT was associated with rapid and substantial pain alleviation. Also, eight (40%) of the patients' wounds healed entirely with TCOT. This study suggests that TCOT may represent a novel pain management device for hard-to-heal wounds.

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analgesia • diabetes • dressing • hard-to-heal leg ulcer • HBOT • hyperbaric oxygen therapy • pain • topical continuous oxygen therapy • topical oxygen therapy • TCOT • TOT • ulcer • venous ulcer • wound • wound healing

Hard-to-heal leg ulcers are a significant medical and socioeconomic problem.[1] Costs related to wound treatment are estimated to be between 2–4% of healthcare budgets in the industrialised world, which is expected to increase due to the ageing population.[1] Even though there are various pathological pathways that lead to hard-to-heal leg ulcers, most of the ulcers are hypoxic and therefore require sufficient oxygen for proper healing.[2] Hypoxia may be favourable for the first stage of wound healing as it initialises physiological responses to promote healing, but prolonged hypoxia, potentiated by enhanced oxygen consumption by neutrophils, prevents wound resolution.[3–5] Oxygen is therefore critical for tissue regeneration, as it helps to upregulate vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2), which results in restoration of macro- and microcirculation as well as connective tissue proliferation.[5–7]

Wound oxygen therapy covers hyperbaric oxygen therapy (HBOT) and topical oxygen therapy (TOT). HBOT is used to treat hard-to-heal leg wounds by delivering 100% oxygen at a pressure 2–3 times higher than atmospheric pressure.[5] HBOT cannot be offered to most patients because it is costly and needs to be applied at specialised centres. The method itself has limitations as it is only applied for a few hours per week, and mostly does not maintain a stable elevated tissue oxygen level. TOT has been introduced in recent years as an alternative to HBOT.

There are currently four types of TOT available: topical pressurised oxygen therapy; wound dressings that release oxygen; topical oxygen emulsion; and topical continuous oxygen therapy (TCOT). This study focused on the last of these.[7,8] TCOT delivers normobaric oxygen through small cannulas or thin tubes to occlusive wound dressings. Portable oxygen generators supply a 24-hour flow of pure oxygen.[9] A recent eight-week trial on 10 patients treated with the Natrox TCOT (Inotec AMD Inc., US) device showed an average wound size reduction of 51%.[4] Further randomised control trials (RCTs) with TCOT on diabetic foot ulcers showed significantly increased healing rates in the group subjected to TCOT.[10,11] However, studies of the analgesic properties of TCOT are currently lacking and are of high importance as hard-to-heal leg wounds are often excruciating and resistant to conventional pain treatment. Pain and wound healing in response to TCOT were examined in the present study.

Method

Data were retrospectively collected from 20 patients who underwent treatment with Natrox TCOT at the Dermato-Venereology Department, Karolinska University Hospital (Stockholm, Sweden). Wound classification was venous, arterial or mixed arteriovenous wounds. A minority of wounds were due to autoimmune

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Table 1. Patient characteristics

ID/age/sex	Comorbidities	Peripheral vascular disease	Wound aetiology
A, 64-year-old male (deceased)	DM II, HTN, aorta/popliteal aneurysms	Yes, microangiopathy	Arterial
B, 79-year-old male	Left leg amputee due to gangrene necrosis, AF, DM II	Yes, venous insufficiency	Arterial
C, 72-year-old male	Essential thrombocytosis (JAK-2 mutation), basilaris ectasia, ischaemic colitis	Yes, deep venous insufficiency	Hydroxycarbamide side-effect
D, 75-year-old male	DM I since 1964	Yes, reduced arterial microcirculation	Arterial
E, 61-year-old female	Factor V Leiden, livedoid vasculopathy and atrophie blanche, eosinophilic fasciitis	Yes, superficial venous insufficiency	Venous
F, 57-year-old male	IgA vasculitis, COPD, migraines	Yes, IgA vasculitis	IgA vasculitis
G, 66-year-old male	HTN	Yes, superficial and deep venous insufficiency with deep vein thrombosis	Venous
H, 66-year-old male	Cardiac comorbidities, cerebrovascular haemorrhage, OSA, DM II, ESRD and morbid obesity	Yes, non-critical bilateral arterial insufficiency	Neuropathic diabetic
I, 83-year-old male	HTN, prostate cancer, monoclonal gammopathy, thrombocytopenia, pyoderma gangrenosum	Yes, superficial venous insufficiency	Venous
J, 66-year-old female	Right-sided Klippel–Trenaunay syndrome with right leg varices	Yes, peripheral and deep AV malformation, arm/leg lymphoedema	Venous
K, 80-year-old female	Klippel–Trenaunay syndrome, HTN, hyperlipidaemia, anaemia	Yes, peripheral atherosclerosis and venous insufficiency	Mixed arteriovenous
L, 52-year-old male	Protein-C deficiency, prior deep vein thrombosis and post-thrombotic syndrome	Venous insufficiency due to post-thrombotic state	Venous
M, 86-year-old female	COPD, pulmonary embolism, hypothyroidism	Yes, venous insufficiency	Venous, hypostatic ulcer
N, 50-year-old male	Atopic eczema, livedoid vasculopathy and depression due to leg ulcers	Yes, deep and shallow venous insufficiency	Venous
O, 13-year-and-5-month-old male	Pansclerotic morphea	None	Pansclerotic morphea
P, 87-year-old female	Osteopenia, aortic insufficiency, former breast cancer patient (curative through surgery)	Yes, shallow venous insufficiency	Venous
Q, 55-year-old male	Psoriatic arthritis, DM II, HTN	None	Probable Ixekizumab side-effect. Granulomatous dermatitis with vasculitis on biopsy
R, 72-year-old female	HTN	Due to mild trauma	Hypertensive wound with disrupted microcirculation
S, 67-year-old male	Ischaemic heart disease, DM II, chronic renal failure, HTN, stroke with minor sequalae	Yes, arterial insufficiency	Ischaemic
T, 40-year-old male	Pyoderma gangrenosum, tricophyton rubrom nails, deep infection with tricomycosis	None	None

AF—atrial fibrillation; AV—arteriovenous; COPD—chronic obstructive pulmonary disease; DM—diabetes mellitus; ESRD—end-stage renal disease; ID—identification; HTN—hypertension; OSA—obstructive sleep apnea

Table 2. Wound description and treatment response with topical continuous oxygen therapy (TCOT)

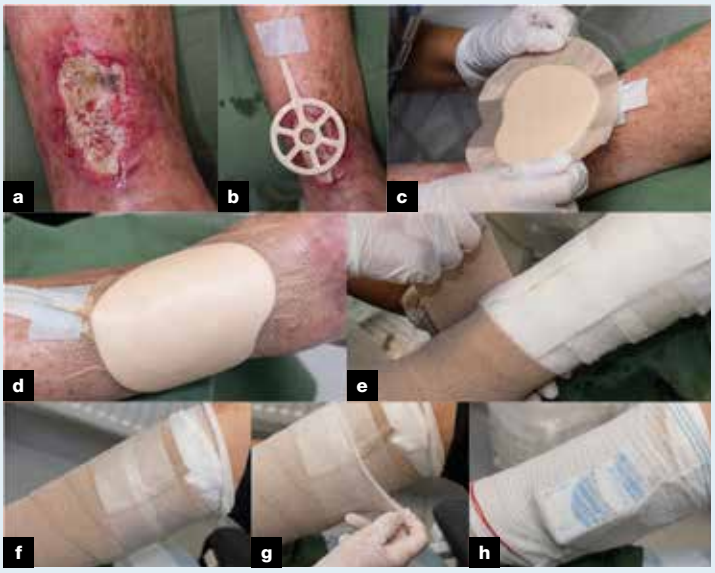
ID	Location	Aetiology and description	Size	1: Wound duration 2: TCOT duration	Complete healing of wound	Concurrent compression therapy	Opioid discontinuation
A	Left leg, lateral malleolus	Arterial, necrotic tissue and blue-toned edges	50.5cm^2 Height 7.7cm Width 8.8cm*	1: 14 months 2. 6 months	Yes	Yes	Yes
B	Right leg, anterior shin, pre-tibia	Arterial, granulation tissue, some fibrin coating and healthy edges	25cm^2 Height 5cm Width 5cm**	1: 29 months 2: 12 months	Yes	Yes	Yes
C	Right leg, ankle, lateral malleolus	Hydroxycarbamide side-effect, viscous, slightly indurated edges	20cm^2 Height 5cm Width 4cm**	1: 20 months 2: 8 months	Yes	Yes	Yes, although uses acetaminophen

Table 2. Wound description and treatment response with TCOT (continued)

ID	Location	Aetiology and description	Size	1: Wound duration 2: TCOT duration	Complete healing of wound	Concurrent compression therapy	Opioid discontinuation
D	Left leg, above the ankle, medially	Arterial, ulceration with erythematous edges Fibrin coated with central necrosis, lightly discharging	4.9cm^2 Height: 2.2cm Width: 2.2cm**	1: 6 months 2: 3 months	Yes	Yes	Yes, but exacerbation after TCOT stoppage
E	Left leg, lateral malleolus	Venous, deep and fibrin coated with raised edges Moderate discharge	2.8cm^2 Height 2.2cm Width 1.7cm*	1: 14 months 2: 6 months	No	Yes	Yes
F	Bilaterally	IgA vasculitis, petechiae and traumatic wound not responding to therapy	Small petechiae and traumatic wound (non-measurable)	1: 22 months 2: 1.5 months	No	Yes	No, only by treating the underlying cause
G	Right leg, medial malleolus	Sparse fibrin and granulation tissue, necrosis in upper wound edges	31.5cm^2 Height 9cm Width 8.8cm*	1: 11 months 2: 8 months	No	Yes	No, oral codeine and paracetamol
H	Right leg, heel	Neuropathic, yellow thin fibrous fibrin with discharge.	3.5cm^2 Height 2.8cm Width 1.9cm*	1: 6 months 2: 1.5 months	Yes	Yes	Yes
I	Right leg, anterior shin	Venous, shallow, thin with focally spread fibrin	33.1 cm^2 Height 7.6cm Width 7.5cm*	1: 30 months 2: <1 month	No	Yes	Yes
J	Right leg, medial malleolus	Venous, dry, fibrin-coated wound	2.1cm^2 Height 2.1cm Width 1.5cm*	1: >24 months 2: 3 months	No	Yes	Yes
K	Right leg, lateral malleolus	Mixed arteriovenous, shallow fibrin tissue	9.7cm^2 Height 4.4cm Width 3.6cm*	1: >24 months 2: 9 months	Yes	Yes	No, oral oxycodone hydrochloride
L	Left leg, medial malleolus	Venous, shallow wound with granulation tissue and abundant fibrin coating at the base	3 wounds: 1. 5cm x 1.7cm 2. 1.5cm x 1.7cm 3. 1cm x 1cm*	1: >24 months 2: Still ongoing	No	Yes	No, still undergoing treatment
M	Left leg, lateral malleolus	Venous, traumatic wound, with no visible granulation tissue Emasculated wound edges	1.2cm^2 Height 1.2cm Width 1.5cm*	1: >24 months 2: 1 month	No	Yes	NA
N	Left leg, medial malleolus Right leg, lateral malleolus	Venous, shallow ulcerations with yellowish crusts Maceration in the wound edges	Height 7cm Width 7cm**	1: 6 months 2: 1 month	Yes	No	Yes
O	Right leg, lateral malleolus	Pansclerotic morphea, clean and shallow, with some crusts	Height 5cm Width 3cm**	1: >24 months 2: 1 month	No	No	NA
P	Left leg, lateral malleolus	Venous, annular wound, depth 4mm, fibrin coated at the base, clean edges	Height 0.5cm Width 0.5cm**	1: 12 months 2: 3 months	No	Yes	NA
Q	Left leg, medial malleolus	Ixekizumab side effect, fibrin coated with violaceous surroundings	Height 7cm Width 4cm**	1: 7 months 2: <1 month	No	Yes	No, treating with prednisolone ceased all pain and led to complete wound healing
R	Left leg, below medial malleolus	Hypertensive wound, small amount of fibrin at the base with a small amount of fibrin tissue. Some maceration in the wound edges	4.7cm^2 Height 2.2cm Width 3.1cm**	1: 3 months 2: 1 month	Yes	Yes	Yes
S	Right leg, at the attachment of the achilles tendon	Ischaemic, thick fibrin coating	Height 3cm Width 2cm**	1: 4 months 2: 2 months	No, almost completely healed	No	Yes
T	Left leg, laterally to malleolus	Relatively deep, thin fibrin coating and granulation tissue Some blue-red wound edges	8.7cm^2 Height 3.8cm Width 3.3cm*	1: 6 months 2: 1 month	No	Yes	NA

* planimetry; ** manual measurement; NA—not applicable (no opioid use); TCOT—topical continuous oxygen therapy

Fig 1. Application of topical continuous oxygen treatment (TCOT) device. The oxygen delivery exhaust is placed directly on the wound and fastened with an adhesive bandage followed by standard compression bandaging. The battery and oxygen electrolysis units are worn outside the bandaging and connected to the exhaust via a tube. Leg ulcer **(a)**; cannula with oxygen efflux **(b)**; adhesive bandage **(c)**; after adhesive bandage placement **(d)**; standard compression bandage placement **(e)**; after bandage placement **(f)**; TCOT device holder **(g)**; TCOT placement **(h)**



diseases and side-effects of drug treatment (Table 1). The oxygen outlet from the device was placed immediately on the wound surface and covered with an adhesive Allevyn gentle border foam dressing (Smith+Nephew AB, Sweden), and compression bandaging was applied to the majority of patients (Fig 1 and Table 2). The mean age of patients was 61 years (range: 13–87 years) and included 14 (70%) male patients and six (30%) female patients. The mean duration of follow-up while treating with TCOT was 3 months 21 days (range: <1–12 months). For wounds that completely healed, the mean duration for follow-up was 5 months 5 days (range: 1–12 months), and for incomplete wound healing, the follow-up period was 2 months 26 days (range: 1–6 months). Follow-up time for ulcers that healed was on average higher than for wounds that did not heal, primarily because wounds that did not exhibit any healing tendency at all stopped TCOT early.

Patients with severe pain and hard-to-heal leg wounds that would not heal within at least three months were included after obtaining informed consent. As these wounds had failed to improve with the standard of care treatment, TCOT was the patients' last resort. Standard of care treatments for hard-to-heal leg ulcers include wound topical analgesia followed by mechanical debridement, wound dressings adjusted to the wound bed status, and compression bandaging adjusted to the arterial circulatory status of the patient.

The primary intention was to evaluate the analgesic effect of TCOT, and the secondary intention was to assess both the wound healing effects and, importantly, whether the wound healed completely.

Pain level was measured by using the Numeric Pain Rating Scale (NPRS scale) before and after completing TCOT treatment.[12] The NPRS scale is an 11-point numerical scale in which 0 equals no pain, 1 the least amount of pain and 10 the worst pain the patient has ever experienced. All patients were given an identification (ID) letter from A–T to anonymise their participation.

Statistics

Paired student's t-test was used to assess differences in pain before and after TCOT treatment using the NPRS scale. Our sample was 20 patients with hard-to-heal leg ulcers in which there had been no other successful treatment for their condition and TCOT was their last resort. A total of 17 patients with painful ulcers were included. The mean NPRS scale value before commencing TCOT was 8.2 ($p \leq 0.0001$) and 1.9 ($p \leq 0.0001$) after TCOT treatment.

Ethics

The study is considered a quality of care study and was approved by the local departmental ethical committee. We conducted a non-preregistered study, with approval from the local institutional review board (IRB), and after receiving informed consent from the study subjects, including consent for publication of photographs.

Results

Before commencing treatment with TCOT, the 17 included patients measured using the NPRS scale all had pain levels >5, and most were in the upper region of the numeric 11-point scale (Fig 2 and 3). The mean NPRS value was eight, with a median of eight before treatment. After TCOT, the mean value was two, and a total of 13 (76%) patients had substantial pain relief, with nine (53%) patients having complete pain regression (Fig 2 and 3). Patient characteristics are shown in Table 1. Wound descriptions, including healing outcomes and opioid discontinuation, are shown in Table 2. Our secondary endpoint was complete healing of the hard-to-heal ulcers and eight (40%) of the wounds completely healed with TCOT. Also, our study showed that the timeline to complete remission of the hard-to-heal ulcer was highly variable, ranging from <1 month to up to 12 months. Adverse effects were reported by four (20%) of 20 patients and included transient pain increase (n=1), wound hypergranulation (n=1) and slight abrasion from the TCOT device (n=2).

The 17 patients with pain included in the study had moderate-to-severe pain before enrolling in the study, and 16 patients were using opioid medications. Notably, out of the total pain cohort who were using opioids (n=16), 11 (69%) patients stopped taking opioids completely after TCOT treatment implementation. TCOT non-responders (n=2) healed their wounds and were free from analgesic medications by treating the

Fig 2. Leg ulcer pain before and after topical continuous oxygen treatment using the numeric pain rating scale (y-axis): individual patient data

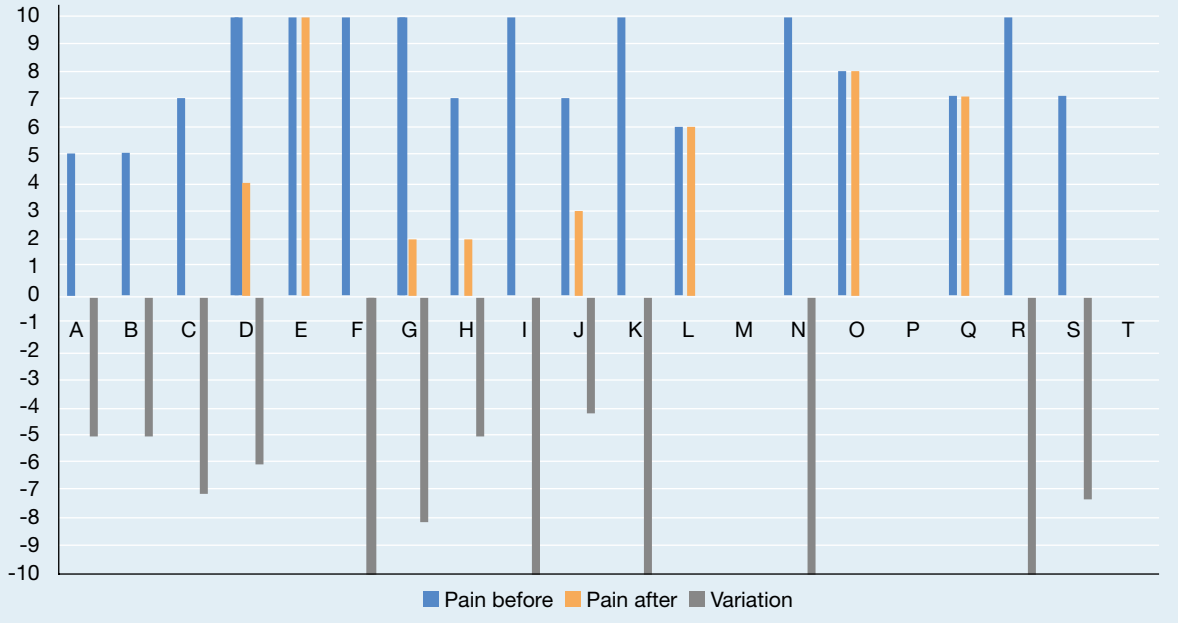
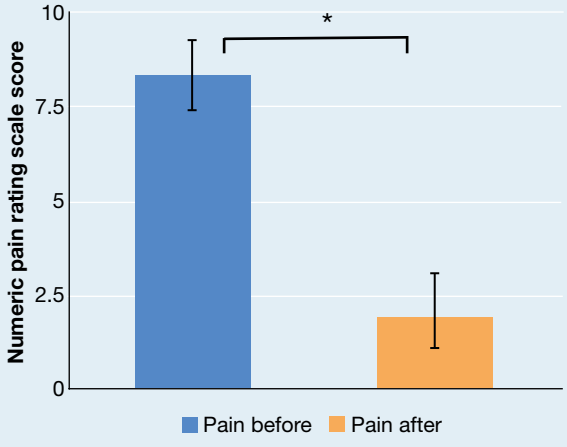


Fig 3. Leg ulcer pain before (mean 8.2) and after (mean 1.9) topical continuous oxygen treatment using the numeric pain rating scale: average patient data
*p<0.00001. Error bars indicate standard error



underlying cause with corticosteroids. Ultimately, two patients still needed opioids, of whom one experienced complete remission of pain while using TCOT and only restarted opioid treatment after discontinuing TCOT.

Discussion

In this study, we demonstrate for the first time that TCOT use in hard-to-heal leg wounds is associated with pain relief, and a reduced need for pharmacological analgesia and concurrent healing. TCOT is compared with other wound pain treatment modalities and we review its potential advantages.

Current therapy for wound pain

In many patients, hard-to-heal leg ulcer pain is inadequately managed, leading to a decreased quality of life.[13] Pain in patients with hard-to-heal wounds is currently mainly treated pharmacologically. The World Health Organization's ladder of pain management, often used when treating patients with chronic pain, recommends acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) as first-line treatments for mild-to-moderate pain.[14] This regimen has been challenged and a study reported that ibuprofen (an NSAID) was superior to acetaminophen. However, it was concluded that drug efficacy varies and that they should be used jointly for optimal effect.[15] Weak and then potent opioids should only be considered for pain that is non-responsive to the first-line pharmacology as they have a well-known potential for misuse and dependency. Tricyclic antidepressants and anticonvulsants, such as amitriptyline and gabapentin, respectively, are generally used for neuropathic pain and are rarely efficient for leg ulcers.[16] Altogether, pharmacological treatment for leg ulcer pain is limited.

RCTs have shown the efficacy of HBOT in treating certain types of hypoxic wounds.[17] However, the analgesic properties of HBOT in hard-to-heal leg wounds have not been investigated to the best of our knowledge. Moreover, HBOT is often not available nor suitable for

Reflective questions

- How effective are current ulcer pain treatments?
- Could topical continuous oxygen therapy (TCOT) be an option for ulcer pain treatment in your practice? If so, why?
- How do different ulcer aetiologies respond differently with TCOT with regard to pain and healing?

many older patients and not a realistic pain treatment alternative for most patients. Besides the lack of access, there are several relative and absolute common contraindications to HBOT.[18] Moreover, transcutaneous electrical nerve stimulation (TENS) is sometimes used for its analgesic effects and wound healing properties.[19] TENS is based on delivering low voltage electrical currents to the skin, which is claimed to inhibit the transmission of nociceptive information at the level of the spinal cord.[20] The European Wound Management Association underlines the need to seek new pain management options, as many options do not give satisfactory results or show undesirable side-effects. This is especially important since there is a strong correlation between patient satisfaction with analgesia and adherence to wound healing treatment and outcome.[21]

Clinical relevance and mechanisms of TCOT

TCOT has several potential advantages. Since it is a local treatment, adverse effects are less likely to occur than with HBOT, which has several potential adverse effects, including barotrauma.[22] In terms of effectiveness, a 14-week non-randomised study of 57 patients showed no reduction in wound size with HBOT, while TCOT applied to 25 patients was associated with a 57% reduction in wound size.[6] Further randomised studies are needed to substantiate these findings. Moreover, the various topical oxygen devices are easily accessible and manageable, and can therefore be provided to primary care patients. This inexpensive treatment could eventually lead to lower treatment costs than HBOT due to less frequent hospital visits and lower device costs.[23]

Our secondary outcome was complete wound remission in which eight (40%) patients had total remission of their hard-to-heal wound. We intend to continue our investigations into wound regression with TCOT and the significant changes in wound size in those who did not have complete remission in subsequent studies. In terms of mechanism, it is appealing that topical oxygen is given continuously as opposed to HBOT, which is given intermittently at specialised centres. Even though the exact analgetic mechanisms of TCOT remain unknown, it may be explained by oxygen's ability to accelerate angiogenesis[17] or by reducing acute ischaemic pain.[24,25] Finally, TCOT may reduce the need for pharmacological analgesia, which is associated with numerous side-effects.

Study limitations

A limitation of this study is that it was not controlled or blinded, so sampling bias or selection bias cannot be excluded. Further studies are therefore needed.

Conclusion

TCOT may be a new treatment modality for hard-to-heal leg ulcer pain and should be recognised as an option in addition to traditional treatment. Also, the affordability and availability are superior compared with HBOT. Thus far, it is unknown which ulcer aetiology satisfactorily responds to TCOT regarding pain and wound healing. However, our study indicates that the patient's improvement in wellbeing and quality of life is vital in those who improve with TCOT. Therefore, there is an incentive to refine our findings further with coming studies to offer TCOT to those eligible for the treatment. JWC

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Notes